



Armed Forces College of Medicine

AFCM



Cardiac fuels and PDH complex

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INTENDED LEARNING OBJECTIVES (ILOs)



➤ **By the end of this lecture, You will be able to:**

1. Illustrate different sources and fates of cardiac fuels.
2. Enumerate sources and fates of pyruvate.
3. Illustrate steps of acetyl CoA synthesis and its regulation.
4. Relate PDH complex abnormalities to clinical and cardiac disorders

Myocardial function depends on a **fine equilibrium** between the **work the heart** has to perform to meet the requirements of the body & the **energy** in the form of **ATP** to sustain excitation-contraction coupling.

Heart failure is a physiological state in which **cardiac output** is **insufficient** to meet the needs of the body and lungs due to **decrease ATP**

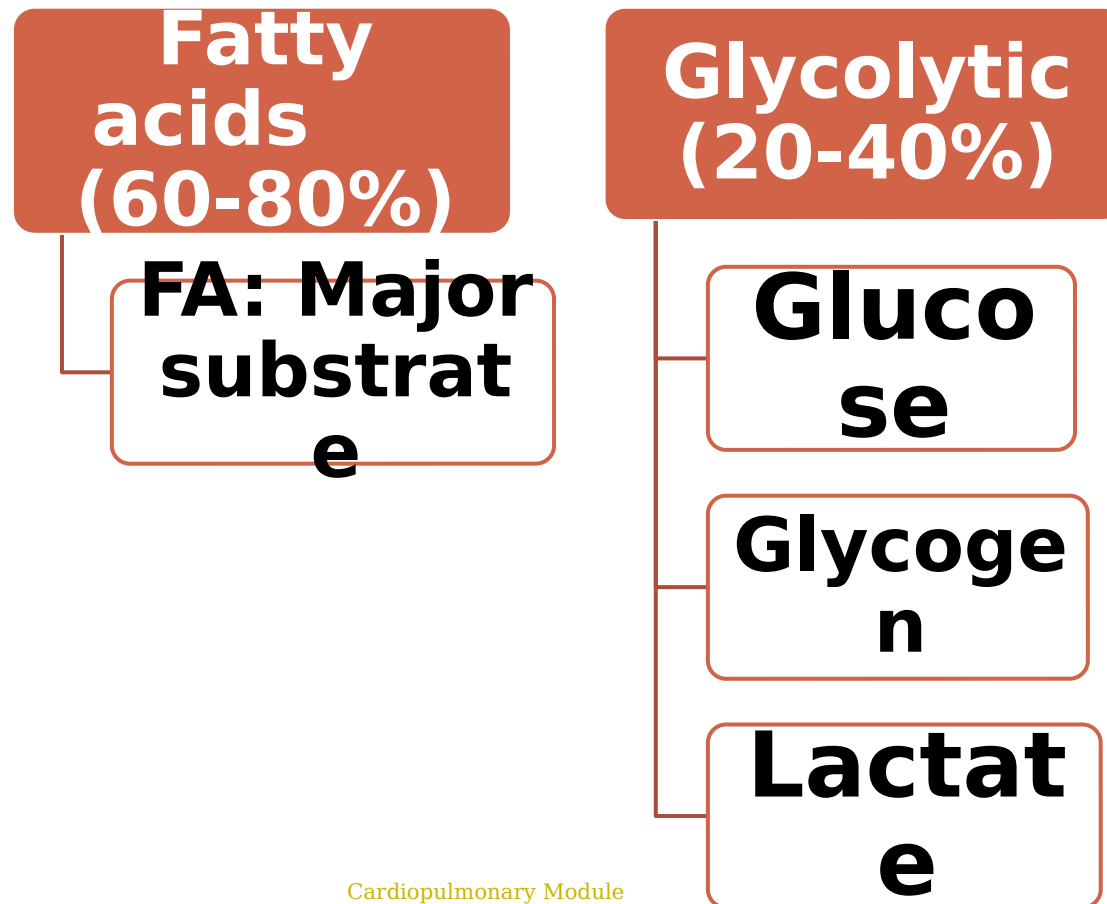
What are the substrates (fuels) of metabolism of the normal heart?

Substrates for oxidative generation of ATP

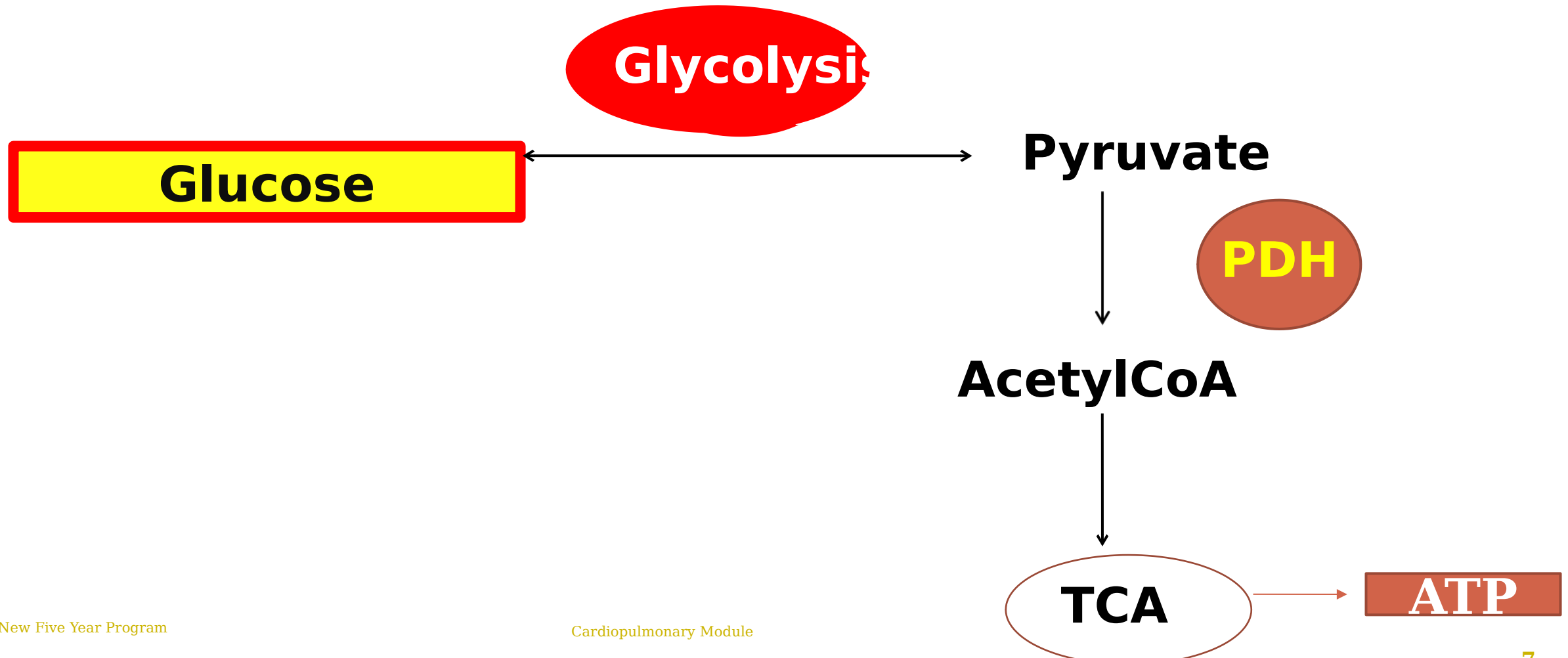
- 1 • **Fatty acids**
- 2 • **Glucose (or Glycogen)**
- 3 • **Lactate**
- 4 • **Ketone bodies**



What are the substrates of metabolism of the normal heart:



What are the fuels of the normal heart?



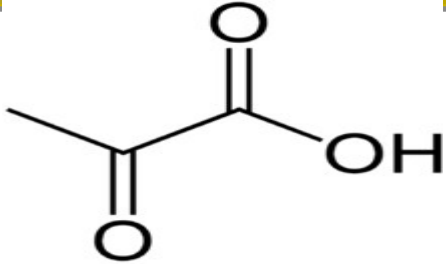
What are the fuels of the normal heart under basal conditions?

- Fatty acids
- Glucose
- Lactate

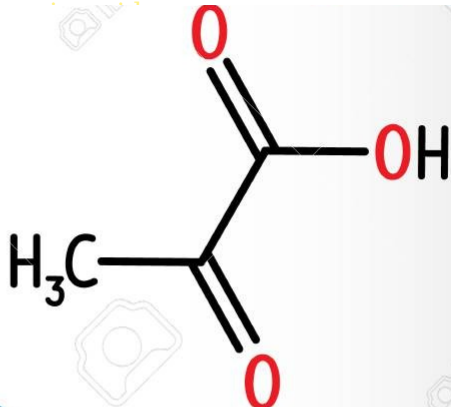


Pyruvic acid Structure

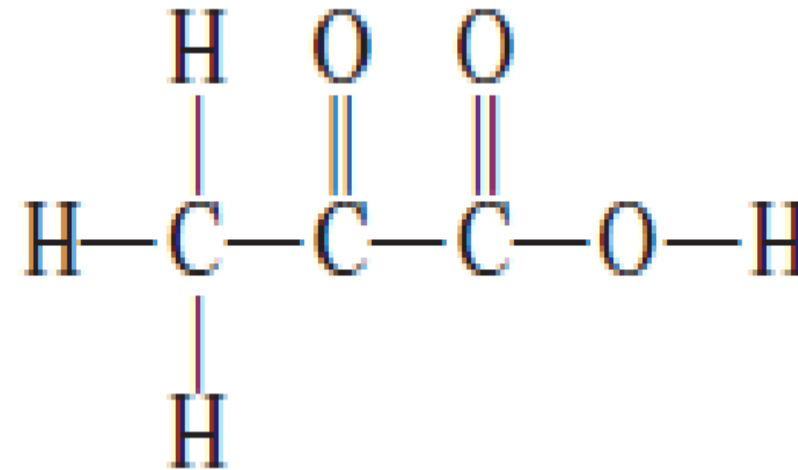
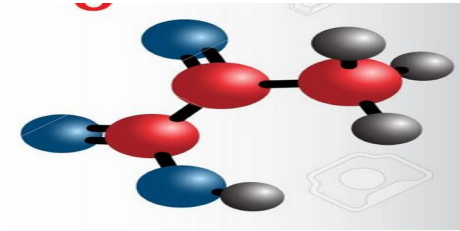
**α- keto
acid**



<https://psychology.wikia.org/wiki/>



https://www.123rf.com/photo_105069068_stock-vector-pyruvic-acid-pyruvate-molecule-it-is-the-simplest-of-the-alpha-keto-acids-structural-chemical-formula.html

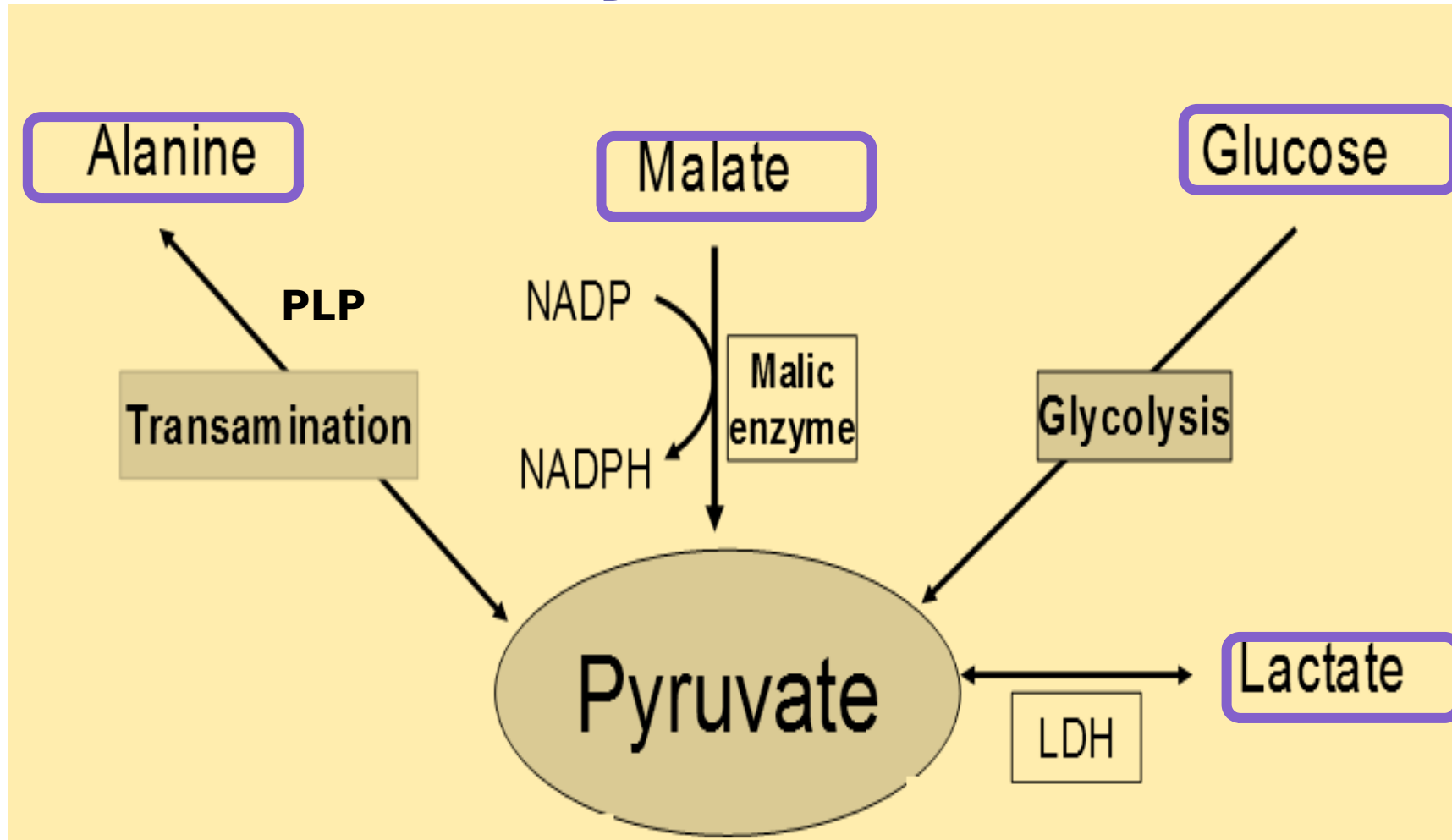


<https://www.bartleby.com/solution-answer/chapter-10-problem-1027ep-general-organic-and-biological-chemistry-7th-edition/9781285853918/pyruvic-acid-which-is-produced-in-metabolic-reactions-has-the-structure-would-you-predict-that/409dca3d-b055-11e9-8385-02ee952b546e>

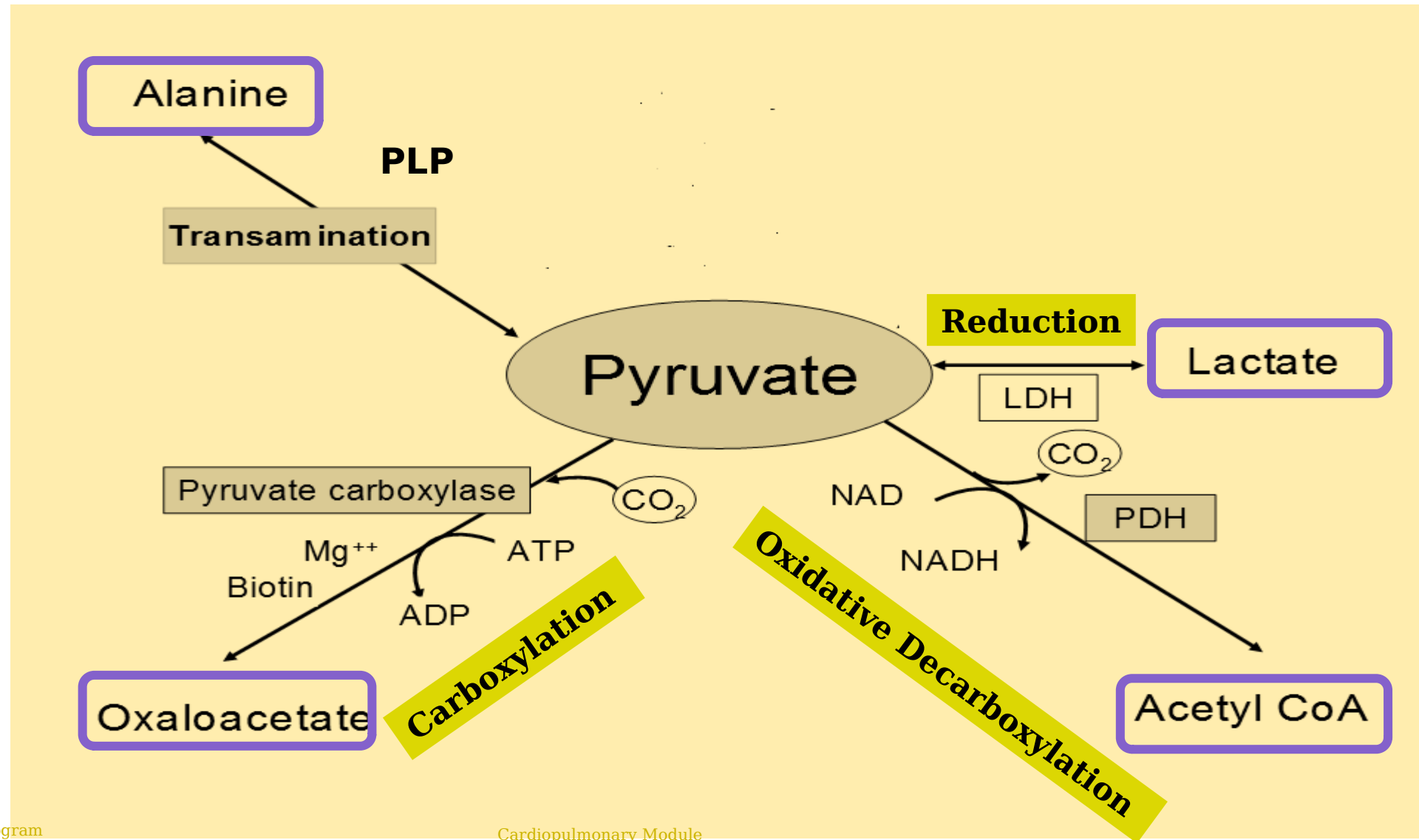
**What are
Sources and
Fates of
Pyruvate**



Sources of Pyruvate

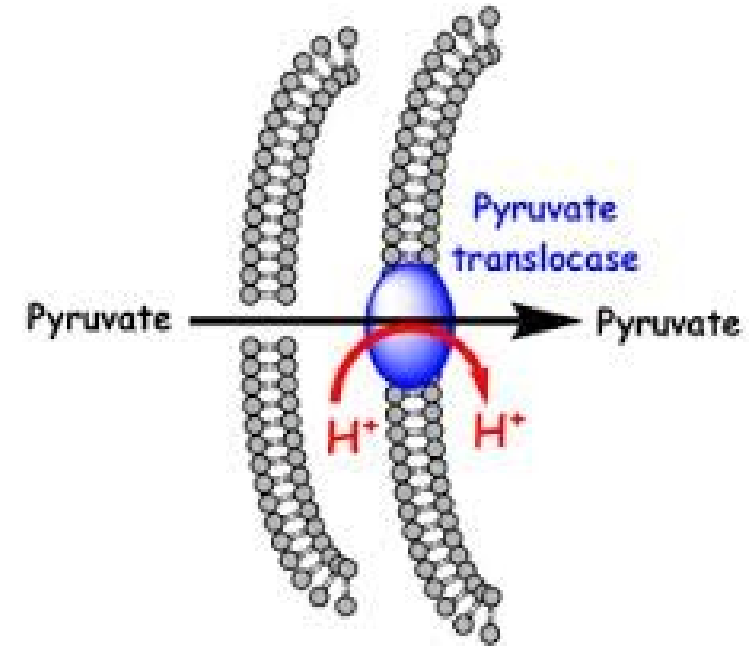


Fates of Pyruvate



Pyruvate Transport

- Pyruvate is transported to the mitochondrial matrix to be completely oxidized in the TCA cycle.



E. Jaspard (2012)

Pyruvate
transporter

<http://biochimej.univ-angers.fr/Page2/COURS/Zsuite/1Respiration/Z999suite/1TransPyrAcetCoA/1TransPyrAcetCoA.htm>

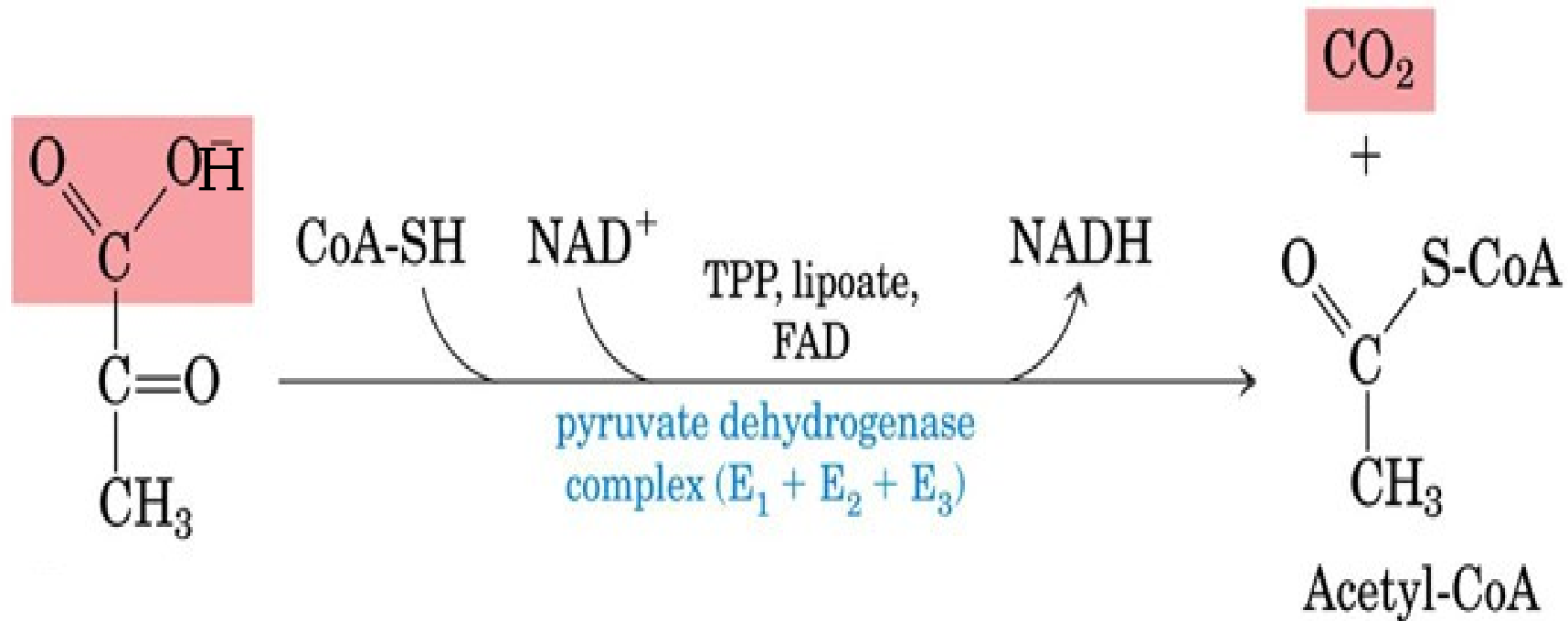
What are the different fates of pyruvate?

1. Reduction into lactate
2. Transamination into alanine
3. Carboxylation into oxaloacetate
4. Oxidative decarboxylation into pyruvate



Oxidative Decarboxylation of Pyruvate

- It occurs by the multienzyme complex pyruvate dehydrogenase (**PDH**)



Edited from: <http://jpkc.scnu.edu.cn/swhx/L/chapt15/Sim0.htm>

Pyruvate Dehydrogenase (PDH)

- **PDH Enzyme *is a Multienzyme complex***
- **Formed of 3 Enzymes+ 5 CoEnzymes**

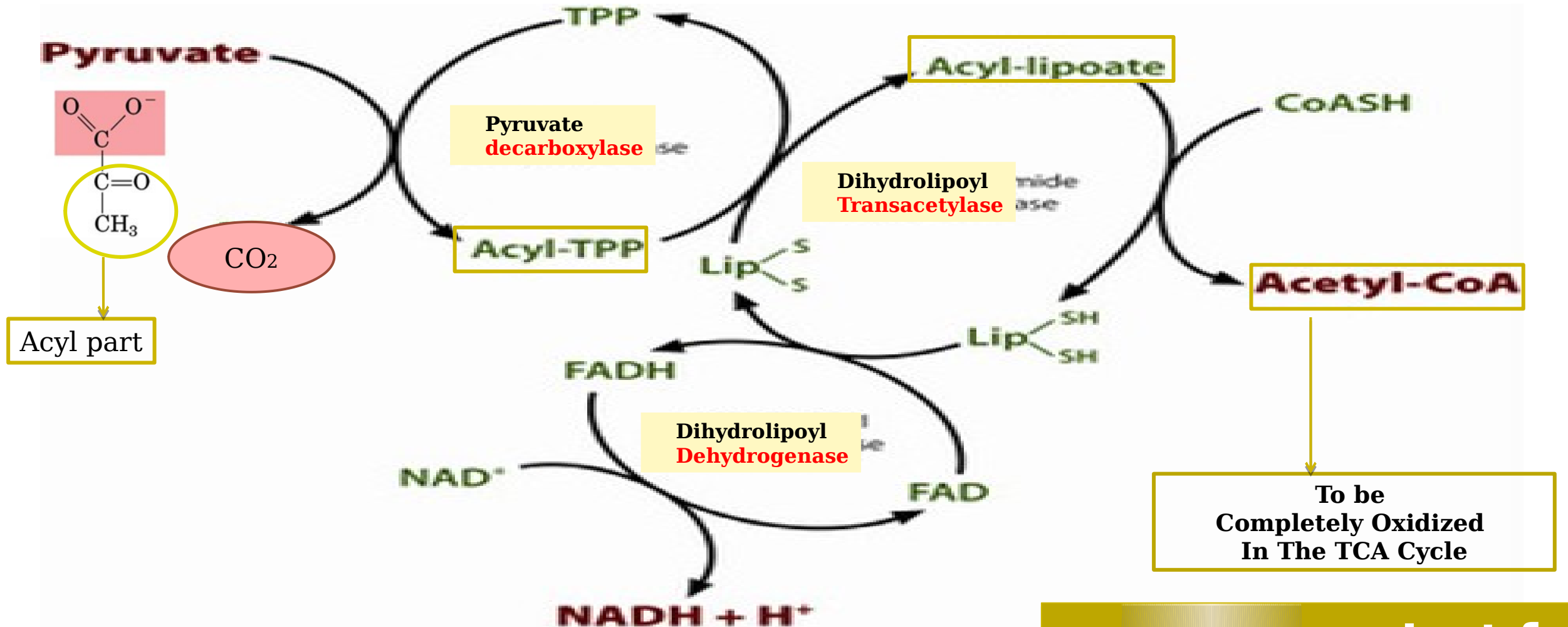
3 Enzymes

- E1 = Pyruvate decarboxylase**
- E2 = Dihydrolipoyl Transacetylase**
- E3 = Dihydrolipoyl Dehydrogenase**

5 Coenzyme

- **TPP**
- **Lipoic acid**
- **CoASH**
- **FAD**
- **NAD**

Pyruvate Dehydrogenase (PDH)



Which vitamin of the following is not a part of pyruvate dehydrogenase?

A. Pantothenic acid

B. Thiamine

C. Niacin

D. Vit. B12



Regulation of (PDH)

Allosteric & Covalent



Covalent Modification of (PDH)

- PDH active in **dephosphorylated** form and inactive in **phosphorylated** form
- Phosphorylation is catalyzed by PDH Kinase (**cAMP independent protein kinase**)

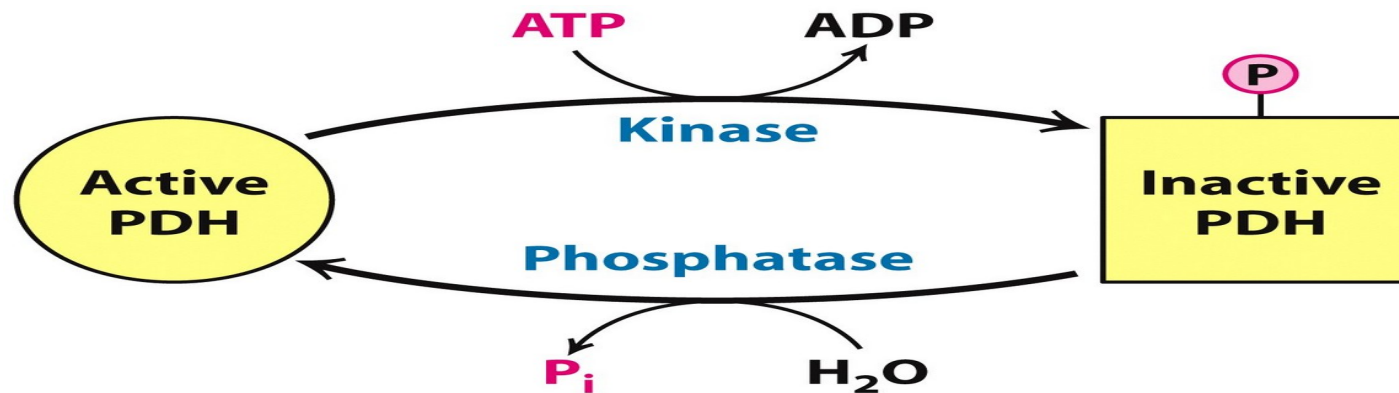


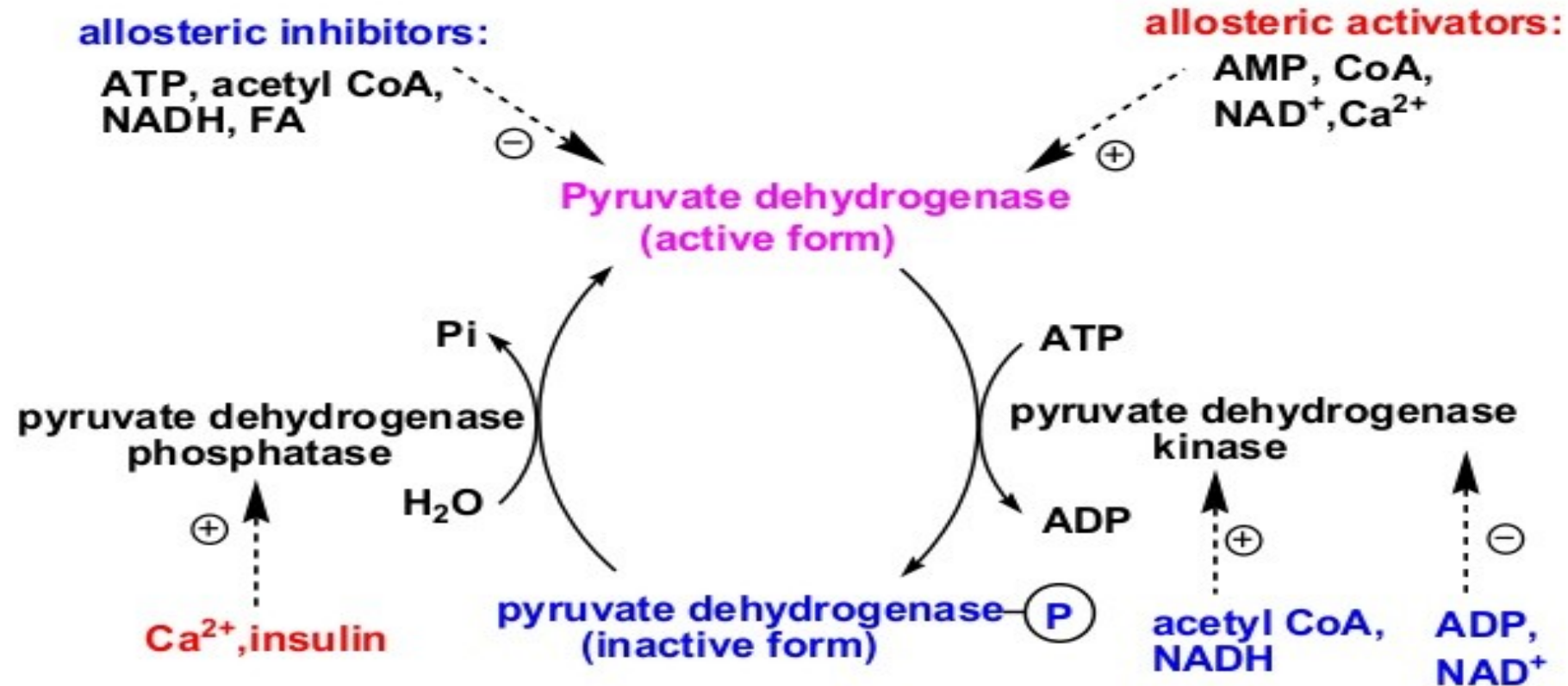
Figure 17.17
Biochemistry, Seventh Edition
© 2012 W. H. Freeman and Company

Allosteric Regulation of (PDH)



Edited from: <https://www.youtube.com/watch?v=WAZXqhtduFw>

(1) Pyruvate dehydrogenase complex



PDH Deficiency

Causes:



1. **Congenital:** congenital lactic acidosis
2. **Dietary deficiency** of TPP (vit B1) → neurologic disturbances.
3. **Alcohol addiction** (affects TPP (vit B1) metabolism)
4. **Arsenite** (contaminated water) and **Mercury poisoning**(mines workers) (binding to the -SH group of the PDH complex)
5. **Cardiac ischemia**

Effects of Inhibition of PDH activity

↓ availability of acetyl CoA
for the TCA cycle

↓ reducing equivalents (as
NADH and FADH₂)

↓ oxidative phosphorylation
in the ETC.

↓ energy supply to the
brain & heart

↑ cytoplasmic
reduction to
lactate or
transamination to
alanine

Lactic acidosis

**Neurological
Manifestations &
heart failure**

↓ Blood flow to the heart



↓ O₂ supply



↓ PDH



↑ Pyruvate



**↑ Lactate
Acidos**



Lactic



Cardiac acidosis



↓ Cardiac contractility & hypotension causing heart failure & shock

**Effect of cardiac
ischemia on PDH
complex and lactic
acidosis**

Signs & symptoms of PDH Deficiency

- **Due to thiamine deficiency PDH complex is inactive → Brain cells are unable to produce sufficient ATP → neurological manifestations called *Wernicke-Korsakoff (encephalopathy-psychosis) syndrome***
- **Lactic acidosis causes nausea, vomiting, breathing problems, abnormal heartbeats**
- **Cardiac acidosis lead to decreased Cardiac contractility & hypotension causing heart failure & shock**

Congenital PDH deficiency manifestations



- **Lactic Acidosis**
- **Hyperammonemia** cause confusion, weakness, fatigue
- **Facial Deformities** Narrow head (microcephaly), prominent forehead, wide nasal bridge
- **Neurological Impairments** (Developmental delays, intellectual impairments, seizures, lethargy (lack of energy), abnormal eye movements, blindness, poor coordination, difficulty walking)
- **Muscular Abnormalities** (Hypotonia (weak muscle tone), **spasticity** (tight muscles), ataxia (abnormal muscle movements))
- **Tachypnea** is a **respiration rate** greater than normal, resulting in abnormally rapid **breathing**

Pyruvate dehydrogenase complex includes all the following EXCEPT:

- a) It is inhibited by arsenite and mercuric ions
- b) It is responsible for oxidative decarboxylation of pyruvate
- ☒ c) It is activated by decreased insulin/glucagon ratio
- d) It is inhibited by kinase enzyme through increased NADH/NAD ratio



Key Points

- The heart can utilize different fuels as sources of energy.
- Pyruvate has diverse sources and fates.
- PDH Enzyme is a Multienzyme complex that can be regulated extensively.
- PDH deficiency has many etiologies and can affect the cardiac function.

SUGGESTED TEXTBOOKS



1- "Lippincott's Illustrated Reviews in Biochemistry" by P.C.Champe, R.A.Harvey and D.R.Ferrier

2- "Harper's Biochemistry" by R.K.Murray, D.K.Granner, P.A. Mayes and V.W.Rodwell.

